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EXAMINER	
KOSSON, ROSANNE	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/564,088	GOJKOVIC, ZORAN	
	Examiner	Art Unit	
	Rosanne Kosson	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,9-22,26-43,46-50 and 55-72* is/are pending in the application.

4a) Of the above claim(s) *10-15,17,18,21 and 26-50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,9,16,19,20,22 and 55-72* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 January 2006* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/18 & 5/24/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group 1, claims 1-9, 16, 19, 20, 22 and 55, drawn to a polynucleotide encoding the polypeptide of SEQ ID NO:2 in the reply filed on April 29, 2008 is acknowledged. Claims 10-15, 17, 18, 21 and 26-50 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to non-elected inventions, there being no allowable generic or linking claim. Claims 1, 4, 5, 7, 10, 11, 13-15, 17, 20-22, 26, 29-32, 39, 43 and 48 have been amended. Claims 8, 23-25, 44-45 and 51-54 have been canceled. Claims 56-72 have been added. Accordingly, claims 1, 2-7, 9, 16, 19, 20, 22, 55-72 are examined on the merits herewith.

In response to Applicant's traversal, the sequence alignment in the middle of p. 6, with GenBank record no. EAA01224, shows that the deoxyribonucleoside kinase has greater than 80% sequence identity to SEQ ID NO:2 over its entire length, 202 of 248 amino acids, for 81.45% sequence identity, as noted in Applicants' response on p. 2. But, Applicant's claims are broad, and, as previously discussed, the common technical feature among the different inventions in the original claims is a polynucleotide "derived" from an *Aedes aegypti* polynucleotide that encodes a multisubstrate deoxyribonucleoside kinase or a protein having at least 80% sequence identity to the protein encoded by the "derived" polynucleotide. Thus, the instant claims lack unity of invention under PCT practice.

Specification

The disclosure is objected to because of the following informality. The specification should be updated to include Applicant's priority information as the U.S. national phase of a

PCT application (PCT/EP2004/051280). Appropriate correction is required.

Drawings

New corrected drawings in compliance with 37 CFR 1.121(d) are required in this application because Figure 1 does not show the features that are described in it according to the specification. Fig. 1 is an alignment of four sequences in which each amino acid is black or white (unboxed), i.e., a white letter in a black box or a normal typed black character, respectively. No gray boxes or shaded boxes are visible to indicate "non-conserved' or "semi-conserved" amino acids (see pp. 5 and 7 of the specification). Applicant is advised to employ the services of a competent patent draftsperson outside the Office, as the U.S. Patent and Trademark Office no longer prepares new drawings. The corrected drawings are required in reply to the Office action to avoid abandonment of the application. The requirement for corrected drawings will not be held in abeyance.

INFORMATION ON HOW TO EFFECT DRAWING CHANGES

Replacement Drawing Sheets

Drawing changes must be made by presenting replacement sheets which incorporate the desired changes and which comply with 37 CFR 1.84. An explanation of the changes made must be presented either in the drawing amendments section, or remarks, section of the amendment paper. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). A replacement sheet must include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of the amended drawing(s) must not be labeled as "amended." If the changes to the drawing figure(s) are not accepted by the examiner, applicant will be notified of any required corrective action in the next Office action. No further drawing submission will be required, unless applicant is notified.

Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and within the top margin.

Annotated Drawing Sheets

A marked-up copy of any amended drawing figure, including annotations indicating the changes made, may be submitted or required by the examiner. The annotated drawing sheet(s) must be clearly labeled as "Annotated Sheet" and must be presented in the amendment or remarks section that explains the change(s) to the drawings.

Timing of Corrections

Applicant is required to submit acceptable corrected drawings within the time period set in the Office action. See 37 CFR 1.85(a). Failure to take corrective action within the set period will result in ABANDONMENT of the application.

If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings MUST be filed within the THREE MONTH shortened statutory period set for reply in the "Notice of Allowability." Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136 for filing the corrected drawings after the mailing of a Notice of Allowability.

Claim Objections

Claim 55, which was placed in Group 1 in the Office action of March 31, 2008, is objected to because of the following informality. This claim depends from claim 10, drawn to a deoxyribonucleoside kinase (Group 2), which is withdrawn for being drawn to a non-elected invention. Claim 55 should be rewritten as an independent claim or rewritten to depend from claim 1. Appropriate correction is required.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 6, 9, 16, 19, 20, 22, 55, 59-63 and 65 and 66 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the

application was filed, had possession of the claimed invention. Specifically, the claims recite a number of very large genera no species of which, or only one of which (SEQ ID NO:1), is disclosed in the specification:

a) polynucleotides encoding a mosquito deoxyribonucleoside kinase that has 80% sequence identity to SEQ ID NO:2 and the complements thereof (one species disclosed, SEQ ID NO:1);

b) polynucleotides encoding a mosquito deoxyribonucleoside kinase or kinase variant that has 80% sequence identity to SEQ ID NO:2 and that decreases at least four-fold the IC_{50} of at least one nucleoside analogue (one species disclosed, SEQ ID NO:1);

c) polynucleotides that hybridize to SEQ ID NO:1 under any conditions (one species disclosed, SEQ ID NO:1);

d) polynucleotides encoding a mosquito deoxyribonucleoside kinase that has 80% sequence identity to SEQ ID NO:2 and that is C-terminally truncated to any degree (no species disclosed, nor is it disclosed how many amino acids may be deleted with the retention of deoxyribonucleoside kinase activity;

e) polynucleotides encoding a mosquito deoxyribonucleoside kinase that has 80% sequence identity to SEQ ID NO:2 and that has amino acid substitutions (replacements) at any number of "non-conserved" or "semi-conserved" amino acid positions (no species disclosed, nor are these positions defined or indicated in the specification relative to SEQ ID NO:1);

f) polynucleotides encoding a mosquito deoxyribonucleoside kinase that has 80% sequence identity to SEQ ID NO:2 and that has amino acid substitutions (replacements) at any number of "corresponding aligned" positions "in another insect kinase" (no species disclosed, these positions are not defined or indicated in the specification relative to SEQ ID NO:1, and of the vast array of insects that exist only three deoxyribonucleoside kinases besides SEQ ID NO:2 are disclosed in the specification);

g) polynucleotides encoding a mosquito deoxyribonucleoside kinase that has 80% sequence identity to SEQ ID NO:2 and that has amino acid substitutions (replacements) at any number of positions at which A, L, I, V, P, M, F and/or W are substituted with any one or more or all of A, L, I, V, P, M, F and/or W with the retention of deoxyribonucleoside kinase activity (no species disclosed);

h) polynucleotides encoding a mosquito deoxyribonucleoside kinase that has 80% sequence identity to SEQ ID NO:2 and that has amino acid substitutions (replacements) at any number of positions at which S, T, Y, N, Q and/or C are substituted with any one or more or all of S, T, Y, N, Q and/or C, in addition to any number of substitutions as described in genus (g), with the retention of deoxyribonucleoside kinase activity (no species disclosed);

i) polynucleotides encoding a mosquito deoxyribonucleoside kinase that has 80% sequence identity to SEQ ID NO:2 and that has amino acid substitutions (replacements) at any number of positions at which K, R and/or H are substituted with any one or more or all of K, R and/or H, in addition to any number of substitutions as described in genera (g) and (h), with the retention of deoxyribonucleoside kinase activity (no species disclosed);

j) polynucleotides encoding a mosquito deoxyribonucleoside kinase that has 80% sequence identity to SEQ ID NO:2 and that has amino acid substitutions (replacements) at any number of positions at which D and/or E are substituted with E and/or D, in addition to any number of substitutions as described in genera (g), (h) and (i), with the retention of deoxyribonucleoside kinase activity (no species disclosed);

k) polynucleotides that hybridize to SEQ ID NO:1 under medium stringency conditions (one species disclosed, SEQ ID NO:1); and

l) polynucleotides that hybridize to SEQ ID NO:1 under medium/high stringency conditions (one species disclosed, SEQ ID NO:1).

The specification discloses zero or one species of each of the claimed genera above, which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genera. A sufficient written description of a genus of polynucleotides may be achieved by a recitation of structural features common to each member (species) of the genus, **which features constitute a substantial portion of each member of the genus**. The only recited structural feature of the genera in these claims (SEQ ID NO: 1) does not constitute a substantial portion of each species in each genus, as the remainder of the structure of any polynucleotide encoding a mosquito deoxyribonucleoside kinase activity is completely undefined, and the specification does not define the remaining structural features necessary for members of the genus to be selected. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

Consequently, there is no evidence that a sufficient number of representative species of these large genera were in the possession of the inventors at the time of filing. To satisfy the written description aspect of 35 U.S.C. 112, first paragraph, for a claimed genus of molecules, it must be clear that: (1) the identifying characteristics of the claimed molecules have been disclosed, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these; and (2) a representative number of species within the genus must be disclosed. Because only zero or one species of each of the claimed genera is disclosed, the claims fail to satisfy the written description requirement.

Claims 1-3, 6-7, 9, 16, 19, 20, 22, 55, 59-63, 65, 66 and 69 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polynucleotide

encoding the polypeptide of SEQ ID NO:2, does not reasonably provide enablement for a polypeptide corresponding to one of the genera listed below:

a) polynucleotides encoding a mosquito deoxyribonucleoside kinase that has 80% or 85% sequence identity to SEQ ID NO:2 and the complements thereof (one species disclosed, SEQ ID NO:1);

b) polynucleotides encoding a mosquito deoxyribonucleoside kinase or kinase variant that has 80% sequence identity to SEQ ID NO:2 and that decreases at least four-fold the IC_{50} of at least one nucleoside analogue (one species disclosed, SEQ ID NO:1, and only one species of the genus of deoxyribonucleoside kinases that decrease at least four-fold the IC50 of at least one nucleoside analogue is disclosed, SEQ ID NO:2);

c) polynucleotides that hybridize to SEQ ID NO:1 under any conditions (one species disclosed, SEQ ID NO:1);

d) polynucleotides encoding a mosquito deoxyribonucleoside kinase that has 80% sequence identity to SEQ ID NO:2 and that is C-terminally truncated to any degree (no species disclosed, nor is it disclosed how many amino acids may be deleted with the retention of deoxyribonucleoside kinase activity;

e) polynucleotides encoding a mosquito deoxyribonucleoside kinase that has 80% sequence identity to SEQ ID NO:2 and that has amino acid substitutions (replacements) at any number of "non-conserved" or "semi-conserved" amino acid positions (no species disclosed, nor are these positions defined or indicated in the specification relative to SEQ ID NO:1);

f) polynucleotides encoding a mosquito deoxyribonucleoside kinase that has 80% sequence identity to SEQ ID NO:2 and that has amino acid substitutions (replacements) at any number of "corresponding aligned" positions "in another insect kinase" (no species disclosed, these positions are not defined or indicated in the specification relative to SEQ ID NO:1, and of the

vast array of insects that exist only three deoxyribonucleoside kinases besides SEQ ID NO:2 are disclosed in the specification);

g) polynucleotides encoding a mosquito deoxyribonucleoside kinase that has 80% sequence identity to SEQ ID NO:2 and that has amino acid substitutions (replacements) at any number of positions at which A, L, I, V, P, M, F and/or W are substituted with any one or more or all of A, L, I, V, P, M, F and/or W with the retention of deoxyribonucleoside kinase activity (no species disclosed);

h) polynucleotides encoding a mosquito deoxyribonucleoside kinase that has 80% sequence identity to SEQ ID NO:2 and that has amino acid substitutions (replacements) at any number of positions at which S, T, Y, N, Q and/or C are substituted with any one or more or all of S, T, Y, N, Q and/or C, in addition to any number of substitutions as described in genus (g), with the retention of deoxyribonucleoside kinase activity (no species disclosed);

i) polynucleotides encoding a mosquito deoxyribonucleoside kinase that has 80% sequence identity to SEQ ID NO:2 and that has amino acid substitutions (replacements) at any number of positions at which K, R and/or H are substituted with any one or more or all of K, R and/or H, in addition to any number of substitutions as described in genera (g) and (h), with the retention of deoxyribonucleoside kinase activity (no species disclosed);

j) polynucleotides encoding a mosquito deoxyribonucleoside kinase that has 80% sequence identity to SEQ ID NO:2 and that has amino acid substitutions (replacements) at any number of positions at which D and/or E are substituted with E and/or D, in addition to any number of substitutions as described in genera (g), (h) and (i), with the retention of deoxyribonucleoside kinase activity (no species disclosed);

k) polynucleotides that hybridize to SEQ ID NO:1 under medium stringency conditions (one species disclosed, SEQ ID NO:1);

l) polynucleotides that hybridize to SEQ ID NO:1 under medium/high stringency conditions (one species disclosed, SEQ ID NO:1) and

m) polynucleotides encoding a mosquito deoxyribonucleoside kinase and having 90% sequence identity to SEQ ID NO:1 (one species disclosed, SEQ ID NO:1)..

As a result, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether or not undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir.1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the breadth of the claims, (2) the nature of the invention, (3) the state of the prior art, (4) the relative skill of those in the art, (5) the predictability or unpredictability of the art, (6) the amount or direction or guidance presented, (7) the presence or absence of working examples, and (8) the quantity of experimentation necessary. Although the quantity of experimentation alone is not dispositive in a determination of whether the required experimentation is undue, this factor does play a central role. For example, a very limited quantity of experimentation may be undue in a fledgling art that is unpredictable where no guidance or working examples are provided in

the specification and prior art, whereas the same amount of experimentation may not be undue when viewed in light of some guidance or a working example or the experimentation required is in a predictable established art. Conversely, a large quantity of experimentation would require a correspondingly greater quantum of guidance, predictability and skill in the art to overcome classification as undue experimentation. In Wands, the determination that undue experimentation was not required to make the claimed invention was based primarily on the nature of the art, and the probability that the required experimentation would result in successfully obtaining the claimed invention. (Wands, 8 USPQ2d 1406). Thus, a combination of factors which, when viewed together, would provide an artisan of ordinary skill in the art with an expectation of successfully obtaining the claimed invention with additional experimentation would preclude the classification of that experimentation as undue. A combination of Wands factors, which provide a very low likelihood of successfully obtaining the claimed invention with additional experimentation, however, would render the additional experimentation undue.

Factors pertinent to this discussion include the predictability of the art, guidance in the specification, the breadth of claims and the amount of experimentation that would be necessary to use the invention.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for vast numbers of multiple substitutions and/or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein, the result of which is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, *e.g.* multiple substitutions. SEQ ID NO:1 is a rather long DNA sequence (747 nucleotides), and the specification does not indicate the individual

amino acids, structural domains or functional domains that must be retained for the retention of the kinase activity of SEQ ID NO:2.

The specification does not support the broad scope of the claims which encompass the genera of polynucleotides listed above, because the specification does **not** establish: (A) regions of the protein structure which may be modified without affecting activity, including the amino acid positions that make up the catalytic or substrate binding site; (B) the general tolerance of deoxyribonucleoside kinases to modification and the extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices are likely to be successful.

Without sufficient guidance, beyond that provided, obtaining a DNA corresponding to one or more of genera (a)-(m) listed above is unpredictable, and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. Applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including the polynucleotides of genera (a)-(m) above. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)).

Further, SEQ ID NO:2 has 248 amino acids. While methods to produce variants of a known sequence such as site-specific mutagenesis, random mutagenesis, etc. are well known to the skilled artisan, producing variants as useful as the native proteins from which the variants are derived requires that one of ordinary skill in the art know or be provided with guidance for the selection of which of the infinite number of variants have the activity. Without such guidance one of ordinary skill would be reduced to the necessity of producing and testing all of the

virtually infinite possibilities. For the rejected claims, because of the size of the proteins, the random making and testing would clearly constitute **undue** experimentation. H. Guo et al. ("Protein Tolerance to Random Amino Acid Change", PNAS 101(25):9205-9210, 2004) teach that the percentage of random single substitution mutations which inactivate a protein for the protein 3-methyladenine DNA glycosylase is 34% and that this number appears to be consistent with other studies in other proteins as well. Guo et al. further show in Table 1 and in Equation 1 that the percentage of active mutants for multiple mutants appears to be exponentially related to this by the simple formula $(.66)^x$ X 100% where x is the number of mutations introduced. Applying this estimate to the instant proteins, for SEQ ID NO:2, 80% identity allows up to 49 mutations, and thus only $(.66)^{49}$ X 100% or 1.44 x 10^{-9}% of random mutants having 80% sequence identity would be active. Consequently, 6.96 x 10^8 clones of mutants would have to be screened to identify one clone that produces an active protein (a protein having the deoxyribonucleoside kinase activity of SEQ ID NO:2). Similarly, 85% identity allows up to 37 mutations, and thus only $(.66)^{37}$ X 100% or 2.10 x 10^{-7}% of random mutants having 85% sequence identity would be active. Consequently, 4.75 x 10^6 clones of mutants would have to be screened to identify one clone that produces an active protein.

Regarding claims to polynucleotides having 90% sequence identity to SEQ ID NO:1, the claims in the elected invention are drawn to the polynucleotides, not the polypeptides. If the claims were drawn to the polypeptides themselves, for a genus of polypeptides having at least 90% sequence identity to SEQ ID NO:2, similarly to the above, 90% identity allows up to 24 mutations, and thus only $(.66)^{24}$ X 100% or 4.67 x 10^{-5}% of random mutants having 90% sequence identity would be active. Consequently, about 21,500 clones of mutants would have to be screened to identify one clone that produces an active protein. While this was physically possible at the time that the invention was made (July 2003), again, the elected claims are

polynucleotide claims. The elected claims encompass polynucleotides having 90% sequence identity to SEQ ID NO:1, a feature which corresponds to 10% of the 747 nucleotides of SEQ ID NO:1 being changed, which amounts to up to 74 changes. 74 changes could be up to 74 amino acid changes. Even assuming that about one third of the nucleotide changes are silent (i.e., don't result in an amino acid change, this feature encompasses up to about 50 amino acid changes, which is about 20% of the amino acids. It would be undue experimentation to screen the required corresponding number of clones in order to find one active one, 6.96×10^6 clones of mutants, as discussed above (and then sequence the encoding DNA in that clone).

Current techniques (i.e., high throughput mutagenesis and screening techniques) in the art would allow for finding a few active mutants within about hundred thousand as is the case for the claims limited to 90% identity on the amino acid sequence level (despite even this being an enormous quantity of experimentation that would take a very long time to accomplish). But, finding a few mutants within the vast, almost infinite numbers of DNA and protein sequences and clones required for screening as in the claims to 80% and 85% sequence identity would not be possible. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has **not** been provided in the instant specification.

In view of the foregoing, the claims fail to satisfy the enablement requirement.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-7, 9, 16, 19, 20, 22, 55-72 are rejected under 35 U.S.C. 112, second

paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. First, claim 1 recites a polynucleotide derived from a yellow fever mosquito. The meaning of this term is unclear, rendering the claims indefinite. It cannot be determined if Applicant means a polynucleotide isolated from a mosquito, or a polynucleotide derived from a polynucleotide of a mosquito, the derived polynucleotide being changed in any way to any to any degree, as the claims and the specification do not define or describe the extent and nature of the change. It cannot be determined if the derived polypeptide is the result of natural mutations or engineered mutations. Appropriate correction is required. Furthermore, the phrase "derived from a yellow fever mosquito" is indefinite as any mosquito may be infected with a microorganism that causes yellow fever. Thus it is unclear what characteristics define a mosquito as a "yellow fever mosquito".

Further, claim 1 is confusing because it recites a Markush group of two polynucleotides that encode a deoxyribonucleoside kinase, (a) SEQ ID NO:1 or a polynucleotide encoding a polypeptide having 80% sequence identity to SEQ ID NO:2 and (b) the complement thereof. But, the polynucleotide in (b) is a complementary strand that does not encode anything. Thus, the two polynucleotides cannot be claimed as a Markush group. Appropriate correction is required. The claim may be rewritten to claim the polynucleotide of (a) or the polynucleotide of (b).

Claim 1(b) is confusing because it cannot be determined if Applicants mean to claim the full-length complementary strand of the polynucleotide in (a) or any fragment of the full-length complementary strand (e.g., all probes and primers). Clarification and appropriate correction are required.

Also, claims 2-3 recite a kinase that is compared to the human herpes simplex virus

(HSV-TK) when the DNA for the two are transfected into eukaryotic cells. The wording of the claim is unclear if the comparison is between the recited kinase and HSV thymidine kinase or between the recited kinase and HSV. Furthermore, it is unclear what property is to be compared and how the comparison is a limitation of the claim. Note, if the claim limitation is intended to be that the presence of the kinase in a cell decreases the IC_{50} of at least one nucleoside analogue by at least 4fold, this does not in fact require any comparison. The DNA encoding the kinase is compared to DNA encoding the herpes virus. Applicants appear to mean that the DNA encoding the kinase and the DNA encoding the human herpes virus 1 thymidine kinase are transfected into cells and that the activities of the two enzymes are compared. Appropriate correction is required.

Claim 6 is indefinite because it recites a polynucleotide that is "capable of hybridizing" to the complement of SEQ ID NO:1, but the claim does not recite the conditions under which the hybridization occurs, rendering the metes and bounds of the claim unclear. Appropriate correction is required. The hybridization conditions must be recited.

Claims 59 and 61 recite the terms non-conserved and semi-conserved amino acid positions. These terms are not defined in the specification, and it cannot be determined how an amino acid position can vary to constitute a conserved, non-conserved or semi-conserved amino acid position. Appropriate correction is required. These terms may be replaced by definite terms that recite exactly which positions in SEQ ID NO:1 or SEQ ID NO:2 may be changed with the retention of function and the nucleotides or amino acids that may be substituted with the retention of function.

Claims 60 and 62 recite the term of amino acid positions that appear at corresponding aligned positions in another insect kinase. It cannot be determined which other insects and which other insect kinases are referred to. It cannot be determined which positions in SEQ ID

NO:2 these amino acid positions are. It cannot be determined which amino acids may be used as the replacements at the "corresponding" positions in SEQ ID NO:2. Appropriate correction is required. The claims may be amended to recite definite amino acid positions in SEQ ID NO:2 that may be replaced with specifically named amino acids that yield a functional deoxyribonucleoside kinase.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1(a), 3, 6, 9, 16, 19, 20, 55 and 59-63 are rejected under 35 U.S.C. 102(a) as being anticipated by Knecht et al. ("Mosquito has a single mutlisubstrate deoxyribonucleoside kinase characterized by unique substrate specificity," Nucleic Acids Res 31(6):1665-1672, March 2003). See also an enclosed Blast 2 alignment of SEQ ID NO:2 with the encoded polypeptide of Knecht et al., GenBank record no. AAO49462, performed on the NCBI Blast website on May 13, 2008. This Blast 2 shows the alignment of the two sequences more clearly than the Blast results sent with the previous Office action.

As previously discussed, Knecht et al. disclose a polynucleotide encoding a mosquito deoxyribonucleoside kinase that has 81.4% sequence identity to SEQ ID NO:2 (202 of 248 amino acids). See p. 1669, right col., and p. 1670, Fig. 3.

Regarding claim 3, the ability of the encoded polypeptide to decrease the IC_{50} of a nucleoside analogue at least four-fold better than Herpes thymidine kinase appears to be an inherent property of the mosquito kinase, rather than the result of a biological or chemical

modification of the mosquito kinase. Thus, the polynucleotides of claims 1 and 3 are the same.

Regarding claim 6, as discussed above, the claim encompasses all hybridization conditions.

Regarding claims 16, 19, 20 and 55, the polynucleotide of Knecht et al. was cloned and expressed to produce protein in an *Anopheles gambiae* cell line, 4a-2s4 cells (see pp. 1669-1670).

Regarding claims 59-62, the kinase sequence from *Anopheles gambiae* is the second sequence shown in Applicants' Fig. 1. Thus, the encoded polypeptide differs from SEQ ID NO:2 by changes at non-conserved and/or semi-conserved positions, as these positions are not defined in the specification but indicated by black letters on a white background in the figure. These changes are replacements at corresponding aligned positions in another insect. The encoded polypeptide of Knecht et al. has a substitution of A for P relative to SEQ ID NO:2 (see enclosed alignment, amino acid position 235 in SEQ ID NO:2 or 233 in the encoded polypeptide of Knecht et al.).

In view of the foregoing, a holding of anticipation is required.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rosanne Kosson whose telephone number is (571)272-2923. The examiner can normally be reached on Monday-Friday, 8:30-6:00, alternate Mondays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Nashaat Nashed can be reached on 571-272-0934. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent

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rk/2008-05-13

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